Original Paper

Pancreatology

Pancreatology 2010;10:702–706
DOI: 10.1159/000320695

Received: June 16, 2010
Accepted: August 20, 2010
Published online: January 18, 2011

Prognostic Value of Endoscopic Ultrasound in Acute Pancreatitis

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Key Words
Endosonography · Pancreatitis · Diagnosis

Abstract
Background/Aims: Endoscopic ultrasonography (EUS) is a useful modality to diagnose causes of pancreatitis. The role of EUS for prediction of pancreatitis severity has not been studied. The aim of this study was to identify the utility of EUS in determining the severity of acute pancreatitis (AP). ***Methods:*** All patients diagnosed with pancreatitis consecutively underwent EUS on the 2nd day of their admission. Atlanta criteria were used as the severity index of pancreatitis. ***Results:*** During the study period, 114 patients (74 females, 40 males; mean age of 53.03 ± 17.7 years) were enrolled in the study. The most common cause of AP was gallstone (78.9%). According to the Atlanta criteria, pancreatitis was mild in 72 (63.2%) and severe in 42 (36.8%) patients. In univariate analysis, the presence of peripancreatic edema, pancreas inhomogeneity, common bile duct dilation and ascites were associated with severe pancreatitis. In multivariate analysis, only the presence of peripancreatic edema in EUS correlated with the severity of AP according to the Atlanta criteria (sensitivity, specificity and accuracy: 65.8, 75.7 and 72.2%, respectively). ***Conclusion:*** EUS may be a new useful imaging modality for prediction of severity of AP and may have prognostic significance in the early phase of AP.

Introduction

Acute pancreatitis (AP) is an inflammatory disease occurring in a previously normal pancreas, and usually has a benign course with low mortality. However, approximately 20% of patients may develop a more severe form of the disease with evidence of organ dysfunction and severe acute pancreatitis (SAP), with mortality rates approaching 30% [1].

Dynamic scoring systems using clinical, biochemical and radiological criteria are useful to identify patients who are developing SAP and may require early support. Overlying intestinal gas and the retroperitoneal location of the pancreas distant from the abdominal wall can impair the visualization of this organ with transabdominal ultrasonography.

Endoscopic ultrasonography (EUS) can show the whole pancreas with details of the parenchymal structure

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and peripancreatic changes as well. In addition, EUS may show the presence of microlithiasis, occult pancreatic malignancies and pancreas divisum, conditions which are not detected easily by transabdominal ultrasonography or CT scan. These conditions can cause and present as AP.

The close proximity of the endoscopic ultrasound probe to the pancreas results in high spatial resolution that is superior to that of CT and MRI. In addition, EUS is a minimally invasive procedure that does not share the relatively high complication rate of endoscopic retrograde cholangiopancreatography. Due to these advantages, EUS has evolved into an important technique in the evaluation of pancreatobiliary disease.

However, the role of EUS in the assessment of the severity of AP is not clear. The aim of this study was to assess the clinical impact of EUS in the prediction of severity of AP.

Methods and Patients

All patients diagnosed with AP and who presented directly to our center consecutively underwent EUS on the 2nd day of their admission. AP was defined as a serum amylase more than 3 times the upper limit of normal associated with epigastric pain, back pain and epigastric tenderness.

The cause of the pancreatitis was determined based on the patient's history of alcohol and drug use, transabdominal ultrasonography, EUS and magnetic resonance cholangiopancreatography.

An abdominal CT scan was performed for patients with clinical SAP (more than 4 days in the hospital or evidence of infection, such as high fever and end organ damages).

The criteria used for the severity index was the Atlanta criteria, with the exception of the APACHE score. Bradley [2] reported the criteria for SAP developed at the international symposium on AP held in Atlanta, Georgia (table 1).

The study was carried out prospectively at a single center by 1 investigator. EUS was performed while the patient was in the left lateral decubitus position under conscious sedation with midazolam (2.5–5 mg) with or without intravenous pethidine (25–50 mg). The uncinate process and head of pancreas were scanned from the duodenum, and the body and tail of the pancreas was scanned from the stomach. All EUS procedures were performed by an expert endosonographer. EUS was performed using a radial echoendoscope (EG-363 DUR, Pentax Optical Co. Ltd., Tokyo, Japan) with a frequency of 7.5 MHz.

In addition to the etiology of pancreatitis, the other variables were assessed by EUS (table 2). Because EUS was performed on the 2nd day of admission, the endosonographer was blinded to either the clinical outcome or the CT findings.

The study was approved by the institutional review board of the Digestive Diseases Research Center of Tehran University of Medical Sciences, according to the Declaration of Helsinki. The investigation was approved by the local ethical committee. Informed consent was obtained according to the guidelines of the institute.

Table 1. Criteria for severe AP (1 or more of the following)

1	Ranson score on admission ≥3 (or during the first 48 h)
2	APACHE II score ≥8 at any time during course
3	Presence of 1 or more organ failures†
4	Presence of 1 or more local complications*

* Includes pancreatic necrosis, pancreatic abscess and pancreatic pseudocyst.

† Organ failures include: shock (systolic blood pressure <90 mm Hg), pulmonary insufficiency (PaO_2 ≤60 mm Hg on room air), renal failure (serum creatinine >2 mg/dl after fluid replacement), gastrointestinal bleeding with >500 ml estimated loss within 24 h, DIC (thrombocytopenia and hypofibrinogenemia and fibrin split products) and severe hypocalcemia (≤7.5 mg/dl).

Patients, depending on their criteria, were divided into mild and severe outcome groups and were statistically compared using χ^2 for categorical variables and Student's t test for continuous variables (data normally distributed). The potential role of risk factors were evaluated by univariate logistic regression analyses and results with a p value of less than 0.20 were entered into the backward multivariable logistic regression model. Collinearity was assessed by correlation analysis between any of the independent variables (correlation coefficient greater than 0.50). Goodness-of-fit in the regression model was evaluated by the Hosmer-Lemeshow test ($p < 0.05$). Adjusted OR with 95% CI were calculated. Statistical analyses were performed using STATA version 8/SE (Stata Corp., College Station, Tex., USA). Statistical significance was set at $p < 0.05$ (2 tails).

Results

From February 2008 to November 2009, 114 eligible patients were recruited. The mean ± SD and median of age were 53.03 ± 17.7 and 55 years, respectively. Most of the patients were women (74 cases, 64.9%). The causes of pancreatitis were the following: gallstone in 90 (78.9%), idiopathic pancreatitis in 9 (7.8%), postendoscopic retrograde cholangiopancreatography pancreatitis in 5 (4.3%), alcohol drinking in 4 (3.5%), periampullary tumors in 3 (3.5%), hypertriglyceridemia in 1 (1.1%) and sphincter of Oddi dysfunction in 2 (1.8%) cases. There were 72 (63.2%) and 42 (36.8%) cases of mild and severe AP, respectively. Differences in EUS findings between mild and severe pancreatitis groups are presented in table 2.

The presence of ascites, pancreatic inhomogeneity, common bile duct (CBD) diameter and peripancreatic edema in the severe pancreatitis group were higher than

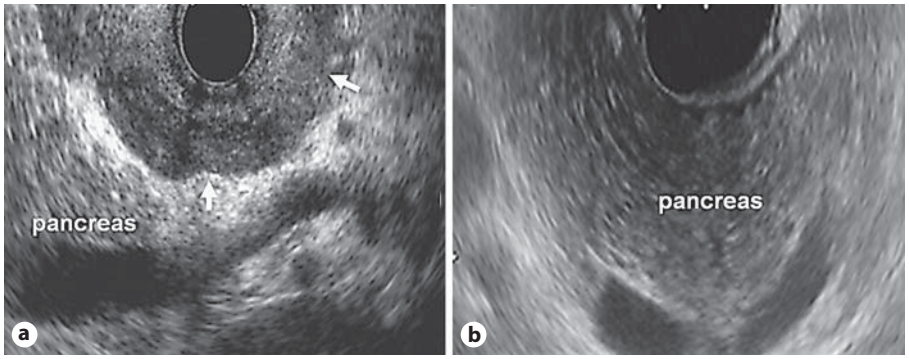

Fig. 1. Peripancreatic edema as a hypoechoic area around the pancreas (arrows, **a**), which is not present in a normal pancreas (**b**).

Table 2. Distribution of EUS variables according to severity of AP (based on the Atlanta criteria)

Variables	Mild pancreatitis (n = 72)	Severe pancreatitis (n = 42)	p
Presence of gall bladder stone(s)	41 (56.9)	28 (66.7)	0.31
Thickened wall gall bladder	27 (37.5)	16 (38.1)	0.95
Duodenal wall thickness	2 (2.8)	0 (0.0)	0.28
Ascites	14 (19.4)	16 (38.1)	0.03
Pancreatic pseudocyst	1 (1.4)	3 (7.1)	0.11
Pancreatic inhomogeneity	18 (25.0)	21 (50.0)	0.007
Pancreas divisum	0 (0.0)	1 (2.4)	0.19
Peripancreatic LAPs	21 (29.2)	9 (21.4)	0.37
CBD stone(s)	18 (25.0)	11 (26.2)	0.89
Difficulty for CBD visualization	9 (12.5)	5 (11.9)	0.93
CBD diameter, mm	5.6 ± 0.3	6.7 ± 0.5	0.047
Pancreatic mass	1 (1.4)	0 (0.0)	0.44
Pancreatic calcification	0 (0.0)	2 (4.8)	0.06
Peripancreatic edema	18 (25.0)	29 (69.0)	<0.0001
PD diameter, mm	2.7 ± 0.1	2.8 ± 0.1	0.42

LAPs = Lymphadenopathies; PD = pancreatic duct.

Table 3. Relationship of EUS variables with SAP (based on the Atlanta criteria) by univariate logistic regression analysis

Variables	OR (crude)	95% CI	p
Presence of gall bladder stone(s)	1.5	0.7–3.3	0.31
Thickened wall gall bladder	1.03	0.5–2.3	0.95
Duodenal wall thickness	–	–	–
Ascites	2.6	1.1–6.0	0.03
Pancreatic pseudocyst	5.5	0.6–54.3	0.30
Pancreatic inhomogeneity	3.0	1.3–6.7	0.008
Pancreas divisum	–	–	–
Peri-pancreatic LAPs	0.7	0.3–1.7	0.37
CBD stone(s)	1.1	0.5–2.5	0.89
Difficulty for CBD visualization	1.0	0.3–3.0	0.93
Increasing 1 mm to the CBD diameter	1.2	1.0–1.3	0.05
Pancreatic mass	–	–	–
Pancreatic calcification	–	–	–
Peripancreatic edema	6.7	2.9–15.6	<0.0001
Increasing 1 mm to the PD diameter	1.2	0.8–1.7	0.43

LAPs = Lymphadenopathies; PD = pancreatic duct.

the mild group based on the Atlanta criteria. The other EUS findings were not significantly different between the 2 groups. All of the EUS variables, based on the Atlanta criteria, were assessed in univariate logistic regression analysis (table 3). In the collinearity assessment phase of multivariate analysis, the presence of ascites and peripancreatic edema were moderately correlated. With the exclusion of ascites, pancreas inhomogeneity and CBD dilation from the model, the final multivariable model was exactly the same. Thus, peripancreatic edema had the highest correlation with pancreatitis severity according to the Atlanta criteria (OR: 5.9, 95% CI: 2.3–15.5). Goodness-of-fit for the final model by Hosmer-Lemeshow statistic (χ^2) was 27.1 ($p < 0.001$). Sensitivity, specificity and accuracy of peripancreatic edema were 65.8, 75.7 and 72.2%, respectively.

Although all patients underwent abdominal ultrasonography before EUS, none of them revealed peripancreatic edema. Thirty-one patients with severe pancreatitis according to the Atlanta criteria had peripancreatic edema in EUS. In the follow-up of these patients, 12 cases were admitted to the ICU with a mean stay of 2 weeks, and 4 cases died because of organ failure and sepsis. Figure 1 shows peripancreatic edema in a patient

with severe pancreatitis compared with a normal pancreas. All patients with severe pancreatitis underwent an abdominal CT scan. These patients had severe pancreatitis (grade C or D), based on the Balthazar CT severity index [3].

Discussion

This study shows that peripancreatic edema in EUS may be a new imaging criterion for the early prediction of pancreatitis severity. Most patients with AP have a benign course and may be safely managed in a general ward. However, early detection of SAP before the development of clinical consequences is important. Thus, it is important to have scoring systems and early predictors of severity and mortality in order to determine which patients might benefit from more intensive care.

Several scoring systems have been used to evaluate the severity of AP based on clinical and laboratory findings, such as Ranson [4] Glasgow [5, 6], APACHE II systems [7] and serum hematocrit [8]. However, each scoring system has its limitations. For example, a meta-analytic Ranson scoring system has poor predictive power for the severity of AP [9]. The APACHE II system cannot define a cutoff between moderate and severe AP [10] and infected and sterile necrosis [11–13]. It also shows a low positive predictive value (43%) for SAP [14].

To our knowledge, this study is the first one that shows the probable utility of EUS in prediction of pancreatitis severity. Another important finding of our study is the prediction of pancreatitis severity in an early phase of AP.

In patients with AP, EUS may be helpful in the diagnosis of occult cholelithiasis, biliary sludge, pancreas divisum, evidence of early chronic pancreatitis or an occult neoplasm, which can present as AP and is not diagnosed easily (if not impossible) by other imaging modalities. In biliary pancreatitis, EUS allows accurate detection of CBD stones and can be used to select patients who will benefit from endoscopic retrograde cholangiopancreatography [15]. Although the majority of CBD stones pass spontaneously, 20–30% of patients with gallstone pancreatitis will have persistent CBD stones that fail to cross the ampulla. Unfortunately, traditional clinical and radiographic criteria used to predict CBD stones, such as elevated liver enzymes and ultrasonography, are nonspecific and unreliable [16–19].

Overlying intestinal gas and the retroperitoneal location of the pancreas distant from the abdominal wall can impair the visualization of this organ with transabdominal ultrasonography. This may be the cause this modality's inability to detect peripancreatic edema.

In the current study, the presence of peripancreatic edema in EUS was correlated with the severity of pancreatitis. In addition, the presence of peripancreatic edema was correlated with grade C and D in the Balthazar CT severity index [3]. Therefore, we can diagnose the cause of pancreatitis as well as to assess the severity of pancreatitis with EUS. In addition, EUS can show pancreatic complications and guide aspiration with a fine needle and/or drainage with stents and a necrosectomy if necessary [20–22]. Thus, EUS may be a 'one-stop shop' procedure in patients with AP.

The other finding of our study is the detection of SAP on the 2nd day of admission, which is very important for choosing more aggressive and earlier care for this high-risk group of patients. As we showed, 31 patients with severe pancreatitis according to the Atlanta criteria had peripancreatic edema on EUS. In the follow-up of these patients, 12 cases were admitted to the ICU with a long duration of stay and 4 cases died because of organ failure and sepsis.

One of the limitations of our study is that abdominal CT was done only for patients with clinical based (not Atlanta-based) severe pancreatitis. However, patients with mild pancreatitis had a benign course and left the hospital without complications.

Moreover, CT scan is not required on the 1st day of AP, unless there are other possible diagnoses. A CT scan is required only in patients who are deteriorating or have SAP, determined clinically and by APACHE II score. It takes a few days for pancreatic necrosis to develop, and treatment is unlikely to be altered based on CT findings. In addition, like ultrasonography, a CT scan is not sensitive for detection of biliary stone or microlithiasis as the main cause of pancreatitis.

Although we have cited some crucial points in favor of EUS, CT remains the accepted standard of reference examination in AP because it is more available than MRI and EUS, and it is more sensitive in detecting calcifications and air bubbles, findings that are not easily detectable by EUS and ultrasonography.

In summary, we showed that EUS could be a new imaging modality for the early prediction of AP severity. However, more studies in other centers are needed to validate the role of EUS in the staging of severity and prognosis of AP.

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